REMARKS

Amendments

The specification has been amended to correct the language of the government funding paragraph and to indicate that the US application listed on page 8 is currently pending.

Claim 1 has been amended to incorporate the limitations of claim 4. Support for the term "precursor miRNA" can be found, for example, in paragraph 15 of the published application.

Claim 4 has been canceled in view of the amendment to claim 1.

Claims 7-10 have been canceled as being directed to a non-elected invention without prejudice to filing a divisional application.

Claim 11 has been amended in the similar manner as claim 1.

Claim 13 has been amended to depend from claim 1 in view of the amendment to claim 1 and the cancellation of claim 4.

Claim 14 has been amended to depend from and be consistent with claim 1 in view of the amendment to claim 1 and the cancellation of claim 4.

New claims 15 and 16 have been added to depend from claim 11 and include the subject matter of prior claims 13 and 14.

It is submitted that these amendments do not constitute new matter, and their entry is requested.

Objection to Specification

The amendment to the specification obviates the objection set forth on page 2 of the Office Action. Withdrawal of this objection is requested.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-3, 5, 6, 11 and 12 under 35 U.S.C. § 103(a) as being obvious over Rossi et al. (US 6,100,087) taken with Billy et al. (*Proc Natl Acad Sci USA* **98**:14428-14433, 2001) and Bernstein et al. (*Nature* **409**:363-366, 2001). The Examiner cites Rossi et al. for

its teaching of the incorporation of a ribozyme into the loop of the adenoviral V1 promoter which contains a BStEII site in an expression vector. He notes that Rossi et al. does not teach using an RNAi molecule which is a substrate for Dicer in the vector. He then cites Billy et al. for its disclosure that RNAi is a substrate for mammalian Dicer and further cites Bernstein et al. for its disclosure that human Dicer generates 22 nucleotide RNAs from dsRNA substrates. Thus, he concludes that it would have been *prima facie* obvious to produce an expression vector comprising an adenoviral VA1 promoter operatively linked to a construct comprising RNAi and to produce a cell containing this vector.

Although Applicants do not agree with the Examiner's contention of *prima facie* obviousness (see further below), Applicants have nevertheless amended claim 1 to include the limitations of claim 4 which was not subject to this rejection. Applicants submit that the claimed subject matter is not obvious from the teachings of Rossi et al., Billy et al. and Bernstein et al.

In view of the above amendments and remarks, Applicants submit that the combination of Rossi et al., Billy et al. and Bernstein et al. does not render the claimed subject matter obvious. Withdrawal of this rejection is requested.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 4 and 13 under 35 U.S.C. § 103(a) as being obvious over Rossi et al. taken with Billy et al. and Bernstein et al. and further in view of Yu et al. (*Proc Natl Acad Sci USA* **99**:6047-6052, 2002). The Examiner cites Yu et al. for its disclosure of an RNA pol III vector comprising shRNA which can inhibit expression in mammalian cells. Thus, he concludes that it would have been *prima facie* obvious to produce an expression vector comprising an adenoviral VA1 promoter operatively linked to a construct comprising RNAi and to produce a cell containing this vector in which the RNAi is an shRNA. Applicants submit that the Examiner is in error in this rejection.

In the combination of Rossi et al., Billy et al. and Berstein et al., the Examiner contends that it would have been *prima facie* obvious to produce an expression vector comprising an adenoviral

VA1 promoter operatively linked to a construct comprising RNAi and to produce a cell containing this vector. By adding Yu et al. to this mix, the Examiner contends that it would have been *prima facie* obvious to produce an RNA Pol III vector comprising shRNA and a skilled artisan would have been motivated to make such a vector as an economic alternative to chemical synthesis of siRNA. However, there is no motivation in the art to make the proposed construct, and in fact, the art itself teaches away from making the proposed construct.

The claimed subject matter is directed to an expression construct in which the adenoviral VA1 promoter is operatively linked to a construct which encodes an shRNA or a precursor miRNA. The primary reference of Rossi et al. is directed to an expression construct in which the adenoviral VA1 promoter is operatively linked to a construct encoding a ribozyme. The transcript of this construct, as taught in Rossi et al., is the VA1 transcript in which the ribozyme is inserted at the top of the stem loop structure of the VA1 transcript. See, Figure 2B of Rossi et al. Rossi et al. further teaches that the ribozyme is not processed from the VA1 transcript, but instead is active as a part of the VA1 transcript. See, column 5, lines 26-33 of Rossi et al. Thus, Rossi et al. teaches that the ribozyme is not cleaved out of the VA1 transcript. Since the ribozyme is not cleaved from the VA1 transcript, this transcript does not appear to be a substrate for mammalian Dicer. Thus, Rossi et al. clearly teaches to the skilled artisan that (a) a construct encoding a ribozyme, an interfering RNA according to the Examiner, operatively linked to a VA1 promoter produces a VA1 transcript containing the ribozyme, (b) the ribozyme is not cleaved from the VA1 transcript and (c) the ribozyme is active without cleavage from the VA1 transcript.

It was well known at the time of filing the present application that shRNA is processed by Dicer to form siRNA of shorter length. See, paragraph 7 of the present application. For example, Bernstein et al. teaches that the siRNAs have a length of 22 nucleotides. Similarly, Yu et al. teaches that the shRNA is processed by Dicer to form an siRNA of about 21 nucleotides. Thus, it was well known to a skilled artisan that it was necessary to process dsRNA, e.g., shRNA, to the shorter length siRNA in order to produce an RNAi molecule that had inhibitory properties on gene expression. Interference was not achieved without the cleavage of the shRNA by Dicer into the smaller siRNA.

As shown in Rossi et al., it was known that the ribozyme in the VA1 transcript was not processed out of the VA1 transcript. There is no disclosure in Rossi et al., or any of the other cited art, to suggest that any RNA inserted into the VA1 transcript would be processed out of the VA1 transcript. In fact, Rossi et al. teaches exactly the opposite effect, namely that an interfering RNA molecule (i.e., ribozyme) is not processed out of the transcript. Because the interfering RNA molecule (i.e., ribozyme) of Rossi et al. is not processed out of the VA1 transcript, there is no motivation to substitute a different interfering molecule, e.g., shRNA which must be cleaved in order to be active, for the ribozyme of Rossi et al. Not only is there no motivation in the cited art to make such a substitution, but there is no suggestion in the art for a skilled artisan to reasonable expect that the shRNA inserted into the VA1 transcript would be cleaved, particularly in view of the specific teachings of Rossi et al. Thus, Applicants submit that the cited prior art teaches away from the presently claimed subject matter and provides no motivation to make the combination proposed by the Examiner in view of this specific teaching away. Consequently, Applicants submit that the claimed subject matter is not obvious from the cited prior art.

In view of the above amendments and remarks, Applicants submit that the combination of Rossi et al., Billy et al., Bernstein et al. and Yu et al. does not render the claimed subject matter obvious. Withdrawal of this rejection is requested.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 4 and 14 under 35 U.S.C. § 103(a) as being obvious over Rossi et al. taken with Billy et al. and Bernstein et al. and further in view of Ambros (*Cell* **107**:823-826, 2001). The Examiner cites Ambros for its disclosure of miRNA. Thus, he concludes that it would have been *prima facie* obvious to produce an expression vector comprising an adenoviral VA1 promoter operatively linked to a construct comprising RNAi in which the RNAi is an miRNA. Applicants submit that the Examiner is in error in this rejection.

In the combination of Rossi et al., Billy et al. and Berstein et al., the Examiner contends that it would have been *prima facie* obvious to produce an expression vector comprising an adenoviral

VA1 promoter operatively linked to a construct comprising RNAi and to produce a cell containing this vector. By adding Ambros to this mix, the Examiner contends that it would have been *prima facie* obvious to produce an RNA Pol III vector comprising shRNA.

As discussed above, Rossi et al. teaches that the ribozyme is not cleaved out of the VA1 transcript. Since the ribozyme is not cleaved from the VA1 transcript, this transcript does not appear to be a substrate for mammalian Dicer. Thus, Rossi et al. clearly teaches to the skilled artisan that (a) a construct encoding a ribozyme, an interfering RNA according to the Examiner, operatively linked to a VA1 promoter produces a VA1 transcript containing the ribozyme, (b) the ribozyme is not cleaved from the VA1 transcript and (c) the ribozyme is active without cleavage from the VA1 transcript.

It was well known at the time of filing the present application that precursor miRNA is processed by Dicer to form miRNA of shorter length of about 22 nucleotides. See, Ambros and Zeng et al. Thus, it was well known to a skilled artisan that it was necessary to process precursor miRNA to the shorter length miRNA in order to produce an RNAi molecule that had inhibitory properties on gene expression. Interference was not achieved without the cleavage of the precursor miRNA by Dicer into the smaller miRNA.

As shown in Rossi et al., it was known that the ribozyme in the VA1 transcript was not processed out of the VA1 transcript. There is no disclosure in Rossi et al., or any of the other cited art, to suggest that any RNA inserted into the VA1 transcript would be processed out of the VA1 transcript. In fact, Rossi et al. teaches exactly the opposite effect, namely that an interfering RNA molecule (i.e., ribozyme) is not processed out of the transcript. Because the interfering RNA molecule (i.e., ribozyme) of Rossi et al. is not processed out of the VA1 transcript, there is no motivation to substitute a different interfering molecule, e.g., precursor miRNA which must be cleaved in order to be active, for the ribozyme of Rossi et al. Not only is there no motivation in the cited art to make such a substitution, but there is no suggestion in the art for a skilled artisan to reasonably expect that the precursor miRNA inserted into the VA1 transcript would be cleaved, particularly in view of the specific teachings of Rossi et al. Thus, Applicants submit that the cited

prior art teaches away from the presently claimed subject matter and provides no motivation to make the combination proposed by the Examiner in view of this specific teaching away. Consequently, Applicants submit that the claimed subject matter is not obvious from the cited prior art.

In view of the above amendments and remarks, Applicants submit that the combination of Rossi et al., Billy et al., Bernstein et al. and Ambros et al. does not render the claimed subject matter obvious. Withdrawal of this rejection is requested.

Rejection for Obviousness-type Double Patenting

The Examiner rejected claims 1, 4, 11-12 and 14 under the judicially created doctrine of obviousness-type double patenting over claims 1, 5 and 9 of U.S. Patent No. 6,100,087 (Rossi et al.) in view of Zeng et al. (*Mol Cell* **9**:1327-1333, 2002). The Examiner cites the claims of Rossi et al. as being directed to a vector comprising an adenoviral VA1 promoter operatively linked to a nucleic acid encoding a ribozyme. The Examiner cites Zeng et al. for its disclosure of natural and designed microRNAs which can inhibit the expression of mRNAs in human cells. The Examiner concludes that it would have been *prima facie* obvious to produce a vector comprising a construct encoding an RNAi molecule, wherein the RNAi molecule is a substrate for mammalian Dicer. Applicants submit that the Examiner is in error in this rejection.

As discussed above, Rossi et al. teaches that the ribozyme is not cleaved out of the VA1 transcript. Since the ribozyme is not cleaved from the VA1 transcript, this transcript does not appear to be a substrate for mammalian Dicer. Thus, Rossi et al. clearly teaches to the skilled artisan that (a) a construct encoding a ribozyme, an interfering RNA according to the Examiner, operatively linked to a VA1 promoter produces a VA1 transcript containing the ribozyme, (b) the ribozyme is not cleaved from the VA1 transcript and (c) the ribozyme is active without cleavage from the VA1 transcript.

It was well known at the time of filing the present application that precursor miRNA is processed by Dicer to form miRNA of shorter length of about 22 nucleotides. See, Ambros and Zeng et al. Thus, it was well known to a skilled artisan that it was necessary to process precursor

miRNA to the shorter length miRNA in order to produce an RNAi molecule that had inhibitory properties on gene expression. Interference was not achieved without the cleavage of the precursor miRNA by Dicer into the smaller miRNA.

As shown in Rossi et al., it was known that the ribozyme in the VA1 transcript was not processed out of the VA1 transcript. There is no disclosure in Rossi et al., or any of the other cited art, to suggest that any RNA inserted into the VA1 transcript would be processed out of the VA1 transcript. In fact, Rossi et al. teaches exactly the opposite effect, namely that an interfering RNA molecule (i.e., ribozyme) is not processed out of the transcript. Because the interfering RNA molecule (i.e., ribozyme) of Rossi et al. is not processed out of the VA1 transcript, there is no motivation to substitute a different interfering molecule, e.g., precursor miRNA which must be cleaved in order to be active, for the ribozyme of Rossi et al. Not only is there no motivation in the cited art to make such a substitution, but there is no suggestion in the art for a skilled artisan to reasonable expect that the precursor miRNA inserted into the VA1 transcript would be cleaved, particularly in view of the specific teachings of Rossi et al. Thus, Applicants submit that the cited prior art teaches away from the presently claimed subject matter and provides no motivation to make the combination proposed by the Examiner in view of this specific teaching away. Consequently, Applicants submit that the claimed subject matter is not obvious from the cited prior art.

In view of the above amendments and remarks, it is submitted that the present claims are not obvious from the combination of Rossi et al. and Zeng et al. Since the present claims are not obvious from the combination of these references, the claims are also not subject to obviousness-type double patenting because there is no obviousness. Withdrawal of this rejection is requested.

Rejection for Obviousness-type Double Patenting

The Examiner rejected claims 1 and 10-11 under the judicially created doctrine of obviousness-type double patenting over claims 1 and 7-9 of U.S. Patent No. 6,995,258 in view of Frey et al. (Benn and Frey, Abstracts of General Meeting of American Society for Microbiology, 92:225, H254, 1992) in view of Zeng et al. Applicants submit that the amendment of claims 1 and

11 obviates this obviousness-type double patenting rejection. Withdrawal of this rejection is requested.

Conclusion

In view of the above amendments and remarks, Applicants believe that the present claims satisfy the provisions of the patent statutes and are patentable over the cited prior art. Reconsideration of the application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite the prosecution of the application..

Respectfully submitted,

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